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RESEARCH ARTICLE

Handedness Correlates with the Dominant Parkinson Side: A Systematic Review and Meta-analysis

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ABSTRACT: Parkinson's disease (PD) characteristically presents with asymmetrical symptoms, contralateral to the side of the most extensive cerebral affection. This intriguing asymmetry, even included in the definition for diagnosing PD, however, is still part of a mystery. The relation with handedness as a common indicator of cerebral asymmetry might provide a clue in the search for causal factors of asymmetrical symptom onset in PD. This possible relationship, however, is still under debate. The objective of this study was to establish whether a relation between handedness and dominant PD side exists. We searched for cross-sectional or cohort studies that registered handedness and onset side in PD patients in PubMed, EMBASE, and Web of Science from their first record until 14 February 2011. Data about handedness and dominant PD side was extracted. Authors who registered both but not described their relation were contacted for further information. Odds ratios (ORs) were analyzed with a fixed effect Mantel-Haenszel model. Heterogeneity and indications of publication bias were limited. Our electronic search identified 10 studies involving 4405 asymmetric PD patients. Of the right-handed patients, 2413 (59.5%) had right-dominant and 1644 (40.5%) had left-dominant PD symptoms. For the left-handed patients this relation was reversed, with 142 (40.8%) right-dominant and 206 (59.2%) left-dominant PD symptoms. Overall OR was 2.13 (95% confidence interval [CI], 1.71–2.66). Handedness and symptom dominance in PD are firmly related with each other in such a way that the PD symptoms emerge more often on the dominant hand-side. Possible causal factors are discussed.

Key Words: Parkinson's disease; epidemiology; handedness; meta-analysis

Parkinson's disease (PD) characteristically presents with asymmetrical symptoms, contralateral to the most extensive affected side of the brain.[1] Although this intriguing aspect of PD is even included in the diagnostic definition, it still remains part of a mystery.[2] As handedness is an established indicator of normal cerebral asymmetry,[3] a possible association between the 2 might provide a clue in the search for causal factors contributing to the onset of this movement disorder. The possible relation between handedness and the dominant side of Parkinson symptoms has been investigated as early as in 1971,[4] while the first support for such relation came in 1972.[5] This association, however, remained an issue of debate as it was replicated[6–9] as well as rejected.[4,10,11]

This standing controversy prompted us to conduct a meta-analysis of the relation between handedness and side of symptoms dominance in PD patients using cohort and cross-sectional studies. We hypothesized that handedness is related to the side of onset in such a way that right-handed patients more often have right-dominant PD symptoms, while left-handed patients more often have left-dominant PD symptoms.

Additional Supporting Information may be found in the online version of this article.

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Methods

Our systematic review was performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria,[12] the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) criteria[13] and the AMSTAR guidelines.[14] No additional review protocol was used.

Search Strategy and Selection Criteria

We searched for cross-sectional or cohort studies that registered handedness as well as dominant side of Parkinson symptoms in the general idiopathic Parkinson population. PubMed, EMBASE, and Web of Science were searched by a researcher (A.H.) and a neurologist/researcher (B.J.) in separate sessions using the search strategy "handedness OR hand OR handed OR handers" AND "Parkinson." Databases were searched from their first records with the latest search on 14 February 2011. No language restriction was applied. Possible inclusion was assessed first based upon title and secondly upon the abstract. The full text was assessed for eligibility if the abstract suggested relevance. References of identified studies and conference abstracts were further hand-searched. We extracted binary data on right- and left-handedness, dominant PD side, PD duration, and age at PD onset. Onset side and worst affected side were both accepted as dominant PD side because onset side is known to generally remain the worst affected side during disease progression.[1] Subjects with mixed-handedness and PD patients with symmetrical affection were not included in registration. We contacted authors of studies that stated their measurement of handedness and dominant Parkinson side, but had not described their relation.

Statistical Analysis

Potential publication bias was assessed by funnel plot. Heterogeneity of the odds ratios (ORs) was evaluated using the chi-square test and the I^2 index. Based on guidelines of the Cochrane Collaboration, we regarded heterogeneity as possibly unimportant when the I^2 value was less than 40% and considerable when more than 75%. We used the standard Mantel-Haenszel fixed effect method to calculate pooled ORs of handedness in relation to the dominant side of PD. A random effects model was considered in case of heterogeneity. Statistical analysis was done with RevMan 5.1 (Cochrane collaboration). Significance level was set at a 2-sided $P < .05$.

Results

Description of Studies

Our electronic search revealed a total of 3476 unduplicated references, of which 10 studies[4,6–11,15–17] were eligible for inclusion in the meta-analysis (Fig. 1). Three studies of the initial 13 included studies were excluded later on. In 1 case we were unable to contact the author of a small study from 1972.[5] Furthermore, 2 studies were excluded because the authors were unable to provide the requested information.[18,19] Characteristics of these 10 included and 3 excluded studies are described in Table 1.

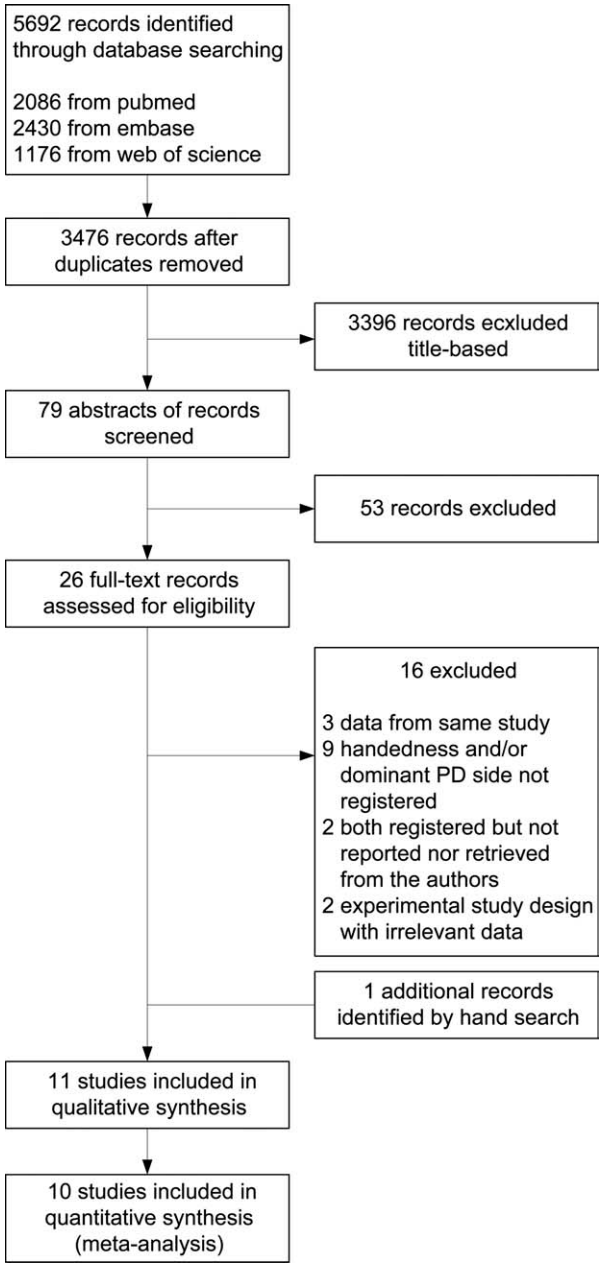

FIG. 1. Flow chart of literature searches.

The 10 included studies concerned 4405 asymmetric PD patients, of whom 2555 (58%) patients were characterized by right-sided symptom dominance PD while 1850 (42%) patients were dominant on the left side. Handedness was right in 4057 (92.1%) and left in 348 patients (7.9%).

TABLE 1. Characteristics of included and excluded studies

	n	Study type	Dominant PD side criteria	Handedness criteria	% Male	PD onset age (y)	PD duration (y)
Included studies							
Akerman et al.[15] (2010)	166	X-sect	Onset and dominant side, patient recall	Current handedness, –	–	–	–
Barrett et al.[6] (2010)	1015	X-sect	Onset side, chart review	Handedness, chart review	61	57	7
Reynolds and Locke[4] (1971)	83	X-sect	Onset side, chart review	Handedness, chart review	74	–	–
Sarwar and Lai[17] (2010)	245	X-sect	Onset side, chart review	Premorbid handedness, chart review	–	–	–
Stewart et al.[16] (2009)	425	X-sect	Onset side, patient recall	Handedness, –	64	58	8
Štochl et al.[10] (2009)	392	X-sect	Onset side, patient recall	Premorbid write-hand, patients recall	59	56	10
Uitti et al.[7] (2005)	1274	Cohort	Onset side, expert exam	Handedness, expert exam	66	63	7
Van der Hoorn et al.[8] (2011)	287	X-sect	Dominant side, chart review	Premorbid write-hand, chart review	58	57	9
Van Rooden et al.[11] (2009)	258	X-sect	Onset side, chart review	Patient recall premorbid AHI scores $\leq$–9 left-handed, and $\geq$9 right-handed	66	49	12
Yust-Katz et al.[9] (2008)	260	X-sect	Onset side, patient recall and right-left difference >4 on UPDRS-III, chart review	Write-hand, patients recall	59	30	7
Excluded studies							
Klawans[5] (1972)	46	X-sect	Onset side, chart review	Handedness, –	–	–	–
Munhoz et al.[18] (2010)	270	X-sect	Onset side, –	Handedness, –	53	53	12
Torres et al.[19] (2010)	302	X-sect	Onset side, expert exam	Handedness, expert exam	58	58	6

PD, Parkinson's disease; X-sect = cross-sectional; AHI, Annett Handedness Inventory; UPDRS, Unified Parkinson's Disease Rating Scale.

Main Analysis

Pooled results from the fixed effect Mantel-Haenszel model showed that PD patients in general have more often PD symptoms on their dominant hand-side. Of the right-handed patients, 2413 (59.5%) had right- and 1644 (40.5%) left-dominant PD symptoms. For the left-handed patients this relation was reversed with 142 (40.8%) right- and 206 (59.2%) left-dominant PD symptoms. The overall OR showed a marked and statistically significant association (2.13; 95% confidence interval, 1.71–2.66; $P < .0001$).

Publication Bias and Heterogeneity

The funnel plot did not reveal indications of a publication bias, as no major asymmetry was shown except the single outlier constituted by a small negative study[4] (Supporting Fig. 1). Neither was a significant heterogeneity present, based upon study characteristics, the forest plot (Fig. 2) and statistical analysis ($P = 0.12$; $I^2 = 36\%$). Again, the study by Reynolds and Locke[4] showed an opposite relationship but the CI was large and included 1.00.

Discussion

By using the statistical strategy of a systematic meta-analysis, we were able to demonstrate a substantial and statistically significant association between the dominant side of PD symptoms and hand-dominance. Right-handed patients showed a significant excess of

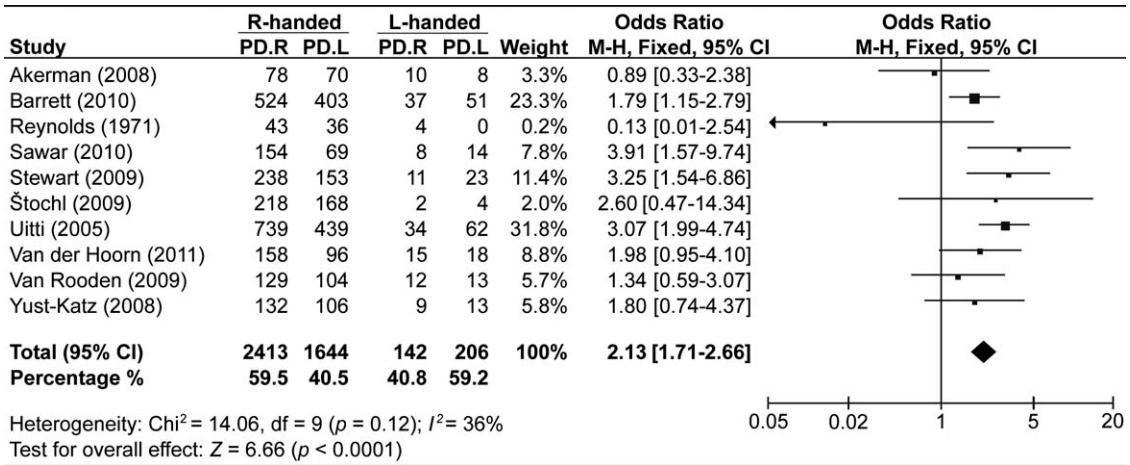

FIG. 2. Forest plot of handedness and dominant PD side. Pooled results of distribution of PD side for right-handed and left-handed patients are shown. PD, Parkinson's disease; PD.R, PD with right-sided symptom dominance; PD.L, PD with left-sided symptom dominance; R-handed, right-handed; L-handed, left-handed; M-H, Mantel-Haenszel; CI, confidence interval.

right-dominant PD symptoms, while the reverse was true for the left-handed patients with a significant excess of left-sided symptoms. The existence of this relation has been controversial as few previous studies have reported this relation,[5–9] whereas others failed to demonstrate it.[4,10,11] No studies, however, reported an inverse relation; ie, an association between dominant hand and the nondominant side of symptoms. This fact in itself already suggested a nonchance relation.

The present meta-analysis resolved methodological issues that may have caused the discrepancy between studies. The small number of left-handed patients in previous studies appeared to have been a major reason for the reported absence of a relation between handedness and lateralized symptom dominance. In the overall population about 10% is estimated to be left-handed,[20] which is consistent with the 8% left-handed patients revealed by our meta-analysis. When comparing the odds of right- and left-handed patients, the OR of previous studies is highly influenced by the small and less precise group of left-handed patients. These small numbers resulted in a lack of statistical power. Pooling of results in the present meta-analysis resolved these issues.

The methodological quality of included studies was similar. Small differences may have arisen by differences in assessing lateralization of PD symptoms and handedness. The latter was determined either by the patient's recall of premorbid handedness or by chart review. Description of the dominant PD side was most often based on the reported side of onset, while in 1 study[8] it was inferred from the consistently reported worst affected side. The 2 variables highly correlate with each other, which have been shown by the fact that the onset side generally remains the worst affected side during disease progression.[1] Moreover, this is an argument against the tentative assumption that patients may notice PD symptoms earlier when using the dominant hand because it is stronger implicated in task-related movement.

As the dominant hemisphere thus appears to be more prone for PD, identification of distinct causal factors becomes a challenging topic. Although lateralization of symptoms may presently remain part of a mystery, the actual association with handedness provides a strong motivation to formulate hypotheses concerning possible causal relations. In this respect one may consider 2 general consequences of lateralized motor control implicated in handedness: (1) hand preference implies an increased metabolic demand with possible negative consequences of oxidative stress in the corresponding (contralateral) hemisphere,[21] while (2) underlying cortical-basal ganglia-thalamic circuitry has an extensive distribution within the dominant hemisphere and runs highly parallel with language networks.[22–24]

With regard to the biochemical characteristics, enhanced oxidative stress may contribute to neurotoxicity inflicted by excitatory neurotransmitters[25,26] as well as dopamine metabolites.[21] Circuitry involved in the referred dominant hemisphere functions comprises particularly ventral parietal-premotor and superior temporal regions,[27] while each of such regions has additional striatum projection.[28] Coherent cortical functioning is facilitated by the cortico-basal ganglia interactions maintained by these projections. The latter give rise to segregated channels through the basal ganglia[29] while strongly interconnected cortical fields have more common striatum projection.[30] Enhanced basal ganglia activity in the dominant hemisphere may thus logically result from the wider extension of functional networks in this hemisphere. Corticostriatal projections are excitatory, which also holds for subthalamic nucleus (STN) projections to the substantia nigra.[31,32] As a consequence, the excitatory drive associated with more widely extended corticostriatal projections and possibly stronger excitatory load converging onto the substantia nigra might lead to excitotoxic effects in the long run of life. This might result in a stronger dopaminergic defect in the dominant compared to the nondominant hemisphere, although the STN innervation of the substantia nigra particularly concerns the pars reticulare and not the pars compacta from which the striatum efferents originate. The primary assumption that normal motor lateralization is associated with an increased level nigrostriatal dopamine turnover in the dominant hemisphere finds support by human in vivo measurements with positron emission tomography (PET).[33] One might, in this respect, even speculate to find asymmetric dopamine cell count.

Conclusions

To conclude, the demonstrated association between handedness and lateralization of PD symptoms is a fact that provides a new challenge to identify causal factors contributing to the onset of PD. ■

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